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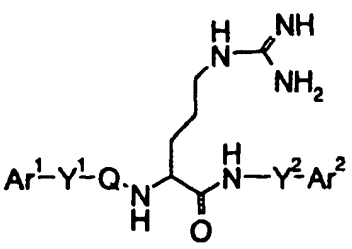
(54) Title: ARGININE DERIVATIVES

(54) 発明の名称: アルギニン誘導体



(57) Abstract: Arginine derivatives represented by the following general formula or medicinally acceptable salts thereof: [wherein Ar^1 and Ar^2 are each independently phenyl, substituted phenyl, naphthyl, substituted naphthyl, or an aromatic heterocyclic group containing one or more atoms selected from among nitrogen, oxygen and sulfur; Y^1 is C_{1-5} alkylene, C_{2-5} alkenylene, or a single bond, with the proviso that the C_{1-5} alkylene may contain a carbon atom substituted with phenyl, substituted phenyl, naphthyl, substituted naphthyl, or C_{1-10} acylamino; Q is carbonyl or sulfonyl; and Y^2 is C_{1-5} alkylene which may contain a carbon atom substituted with phenyl, substituted phenyl, naphthyl, substituted naphthyl, hydroxyl, carbamoyl, mono(C_{1-5} alkyl)amido, or di(C_{1-5} alkyl)amido]. Peptidic ligands are provided, which have affinity and specificity for MC_4 receptor.

[続葉有]

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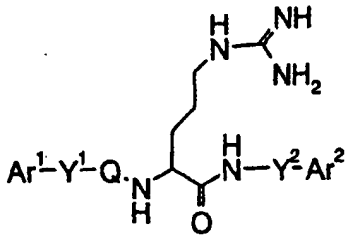
(57) 要約:

式



[式中、Ａｒ¹及びＡｒ²は同一又は異なって、フェニル基、置換フェニル基、ナフチル基、置換ナフチル基、又は窒素、酸素若しくは硫黄原子を一つ以上含むヘテロ芳香環基を示し、Ｙ¹はＣ₁₋₆アルキレン基、Ｃ₂₋₆アルケニレン基又は単結合を示し、該Ｃ₁₋₆アルキレン基はフェニル基、置換フェニル基、ナフチル基、置換ナフチル基、又はＣ₁₋₁₀アシルアミノ基で置換された炭素原子を含んでもよく、Ｑはカルボニル基又はスルホニル基を示し、Ｙ²はＣ₁₋₆アルキレン基を示し、該Ｃ₁₋₆アルキレン基はフェニル基、置換フェニル基、ナフチル基、置換ナフチル基、水酸基、カルバモイル基、モノ－Ｃ₁₋₆アルキルアミド基又はジ－Ｃ₁₋₆アルキルアミド基で置換された炭素原子を含んでもよい。]で表されるアルギニン誘導体又はその医薬上許容される塩。

ＭＣ₄受容体に親和性及び特異性を有するペプチド性リガンドを提供する。

W1285-07
EPC

I, Masanori KOMATSU , a national of Japan, c/o Asamura Patent Office of 331-340, New Ohtemachi Building, 2-1, Ohtemachi-2-chome, Chiyoda-ku, Tokyo, Japan, declare that to the best of my knowledge and belief the attached is a full, true, and faithful translation into English made by me of Japanese Patent Application No. 2001-144659 .

Signed this 10th day of March , 2004 .

Masanori KOMATSU

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The Patent Office

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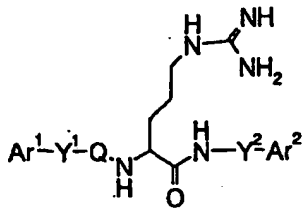
[Title of the Invention] ARGININE DERIVATIVES

[Scope of Claim for a Patent]

[Claim 1] An arginine derivative represented by the formula:

[Formula 1]



[wherein Ar^1 and Ar^2 may be the same or different, and are each a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, or a heteroaromatic ring containing one or more of nitrogen, oxygen and sulfur atoms; Y^1 is a C_{1-5} alkylene group which optionally contains a carbon atom substituted with a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, or a C_{1-10} acylamino group, and optionally contains a double bond in the main chain, or a single bond; Q is a carbonyl group or a sulfonyl group; Y^2 is a C_{1-5} alkylene group which optionally contains a carbon atom substituted with a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, a hydroxyl

group, a carbamoyl group, or an amide group having one or two of C_{1-5} alkyl groups on the nitrogen atom], or a pharmaceutically acceptable salt thereof.

[Claim 2] A medicine comprising the arginine derivative or a pharmaceutically acceptable salt thereof according to Claim 1.

[Claim 3] Use of the arginine derivative or a pharmaceutically acceptable salt thereof according to Claim 1 as a ligand for MC_4 receptor.

[Detailed Description of the Invention]

[0001]

[Technical Field Pertinent to the Invention]

The present invention relates to novel arginine derivatives which are ligands for MC_4 receptor.

[0002]

[Prior Art]

Melanocortins (α-, β- and γ-MSH's, and ACTH) are reported to be biosynthesized in the brain from the processing of POMC, their precursors, and to be pertinent to various physiological functions (Nature, 278, 423, 1979). Melanocortins generate the physiological functions by binding with the specific receptor. Currently, melanocortin receptors (MC receptors) are classified into 5 subtypes of MC_1 - MC_5. Among these receptors, MC_4 receptor is recognized to appear specifically in the brain, and to be widely distributed in the brain (J. Biol. Chem., 268, 15174,

1993; Mol. Endocrinol., 8, 1298, 1994).

[0003]

Recently, the relation among MC_4 receptor, the appetite and the obesity has been suggested. It has been reported that, in the animal tests using selective peptidergic agonists and antagonists for MC_4 and MC_3 receptors, a strong anorectic action was observed in fast mice and various obesity models (Nature, 385, 165, 1997). In addition, remarkable increases in the body weight, the blood insulin content and the glucose content have been observed in MC_4 receptor KO mice (Cell, 88, 131, 1997), and it was suggested that MC_4 receptor acts to control the feeding behavior and the obesity.

On the other hand, it is recognized that MC_4 receptor is also widely distributed in the limbic system (e.g., the hippocampus and amygdaloid body) and the raphe nuclei which is the origin nuclei of the serotonin nerve as well as the hypothalamus which is deeply pertinent to feeding behavior (Mol. Endocrinol., 8, 1298, 1994). It has further been recognized in the animal tests that ACTH and α-MSH act to body temperature regulation (Brain Res., 18, 473, 1987), to blood pressure (Am. J. Physiol., 257, R681, 1989), to neuroendocrine system (Life Sci., 25, 1791, 1979), to learning/memory (Neurosci. Biobehav. Rev., 4, 9, 1980) and to awaking (Neurosci. Biobehav. Rev., 4, 9, 1980), and reported to cause anxiety-like symptom and the

activation of hypothalamus-pituitary-adrenal system (Pharmacol. Biochem. Behav., 36, 631, 1990; Peptides, 17, 171, 1996; ibid. 11, 647, 1990; ibid. 11, 915, 1990; Pharmacol. Biochem. Behav., 12, 711, 1980). However, ACTH and α-MSH are subtype non-specific agonists, and the relation of melanocortin receptor subtypes and these physiological functions has not yet been clarified.

Peptidergic agonists and antagonists have been reported to MC_4 receptor (Nature, 385, 165, 1997), but they also have the affinity to MC_3 receptor, and cannot be used for MC_4 receptor as a selective ligand. In addition, specific ligands to MC_4 receptor have not been reported at all. Accordingly, among MC receptors, there has not yet been clarified the physiological function via MC_4 receptor which appears specifically in the brain and is widely distributed in the brain.

[0004]

[Problem to be solved by the Invention]

An object of the present invention is to provide peptidergic ligands which have the affinity and specificity to MC_4 receptor.

[0005]

[Means for Solving Problem]

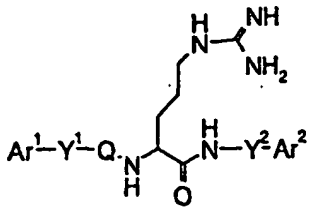
As a results of an extensive research on arginine derivatives, the present inventors have found arginine derivatives which are ligands having the affinity to MC_4 receptor, and thereby the present invention has been accomplished.

The present invention is illustrated below.

The present invention is directed to an arginine derivative represented by the formula:

[0006]

[Formula 2]



[I]

[0007]

[wherein Ar^1 and Ar^2 may be the same or different, and are each a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, or a heteroaromatic ring containing one or more of nitrogen, oxygen and sulfur atoms; Y^1 is a C_{1-5} alkylene group which optionally contains a carbon atom substituted with a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, or a C_{1-10} acylamino group, and optionally contains a double bond in the main chain, or a single bond; Q is a carbonyl group or a sulfonyl group; Y^2 is a C_{1-5} alkylene group which optionally contains a carbon atom substituted with a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, a hydroxyl group, a carbamoyl group, or an amide group having one or two of C_{1-5} alkyl groups on the nitrogen atom], or a

pharmaceutically acceptable salt thereof.

In the present invention, the substituted phenyl group refers to a phenyl group substituted with 1 to 3 substituents arbitrarily selected from the group consisting of a C_{1-5} alkyl group, a C_{1-5} alkoxy group, an aralkyloxy group, a hydroxyl group, a halogen atom, a nitro group, an amino group which is substituted with one or two of C_{1-5} alkyl groups or unsubstituted, a trifluoromethyl group and a phenyl group; and examples of which are a 2-methylphenyl group, a 3-methylphenyl group, a 4-methylphenyl group, a 2-ethylphenyl group, a 3-ethylphenyl group, a 4-ethylphenyl group, a 2-propylphenyl group, a 3-propylphenyl group, a 4-propylphenyl group, a 2-cyclopentylphenyl group, a 2-methoxyphenyl group, a 3-methoxyphenyl group, a 4-methoxyphenyl group, a 4-ethoxyphenyl group, a 4-isopropoxyphenyl group, a 4-benzyloxyphenyl group, a 4-hydroxyphenyl group, a 2-fluorophenyl group, a 3-fluorophenyl group, a 4-fluorophenyl group, a 2-chlorophenyl group, a 3-chlorophenyl group, a 4-chlorophenyl group, a 2-bromophenyl group, a 3-bromophenyl group, a 4-bromophenyl group, a 4-nitrophenyl group, a 4-trifluoromethylphenyl group and a 4-biphenyl group.

[0008]

The substituted naphthyl group refers to a naphthyl group substituted with 1 to 3 substituents arbitrarily selected from the group consisting of a C_{1-5}

alkyl group, a C_{1-5} alkoxy group, an aralkyloxy group, a halogen atom, a nitro group, an amino group which is substituted with one or two of C_{1-5} alkyl groups or unsubstituted, a trifluoromethyl group and a phenyl group; and an example of which is a 5-dimethylaminonaphthyl group.

The heteroaromatic ring containing one or more of nitrogen, oxygen and sulfur atoms refers to a monocyclic or dicyclic aromatic ring which contains one or more of nitrogen, oxygen and sulfur atoms; and examples of which are a 2-pyridyl group, a 3-pyridyl group, a 4-pyridyl group, a 3-indolyl group, a 3-benzothienyl group and a 4-imidazolyl group.

[0009]

The C_{1-10} acylamino group refers to an amino group substituted with a straight, branched or cyclic C_{1-10} acyl group; and examples of which are a formylamino group, an acetylamino group, a propionylamino group, a butyrylamino group, an isobutyrylamino group, a valerylamino group, an isovalerylamino group, a pivaloylamino group, a benzyloxycarbonylamino group and a t-butoxycarbonylamino group.

The C_{1-5} alkyl group refers to a straight, branched or cyclic alkyl group; and examples which are a methyl group, an ethyl group, a propyl group, an isopropyl group, a cyclopropyl group, a butyl group, an isobutyl group, a cyclobutyl group, a cyclopropylmethyl

group, a pentyl group, an isopentyl group, a cyclopentyl group, a cyclobutylmethyl group and a 1-ethylpropyl group.

The C_{1-5} alkoxy group refers to a straight, branced or cyclic alkoxy group; and examples of which are a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, a cyclopropylmethoxy group, a pentyloxy group and an isopentyloxy group.

The amino group substituted with one or two of C_{1-5} alkyl groups refers to an amino group substituted with one or two of straight, branched or cyclic alkyl groups; and examples of which are a methylamino group, an ethylamino group, a propylamino group, a dimethylamino group, a diethylamino group and a dipropylamino group.

The halogen atom refers to a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

[0010]

[Mode for Carrying Out the Invention]

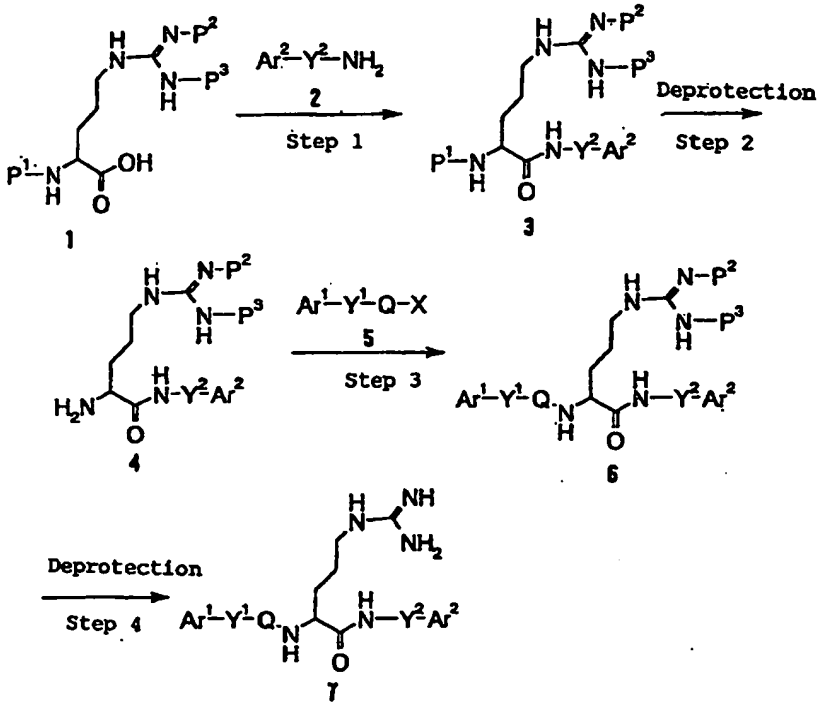
The compounds of Formula [1] can be prepared by the following general preparation method (in the following reaction schemes, Ar^1, Ar^2, Y^1, Y^2 and Q are as defined above; X is a hydroxyl group, a chlorine atom, a bromine atom or an iodine atom; P^1 is an ordinary amino-protective group such as a t-butoxycarbonyl group or a benzyloxycarbonyl group; P^2 and P^3 are each an ordinary guanidino-protective group

such as a t-butoxycarbonyl group, a benzyloxycarbonyl group, a nitro group, a tosyl group or a 2,2,5,7,8-pentamethylchroman-6-sulfonyl group).

[General preparation method]

[0011]

[Formula 3]



[0012]

[Step 1]

Compound (1) can be coupled with compound (2) in the presence or absence of a base in an inert solvent to convert to compound (3).

The base includes, for example, organic amines (e.g., triethylamine, diisopropylethylamine, pyridine

and N-methylmorpholine) and inorganic bases (e.g., potassium carbonate and sodium bicarbonate). The coupling includes, for example, an amidation via an acid halide(e.g., an acid chloride and an acid bromide), an amidation via a mixed acid anhydride using ethyl chlorocarbonate, isobutyl chlorocarbonate, etc., and an amidation using a coupling agent such as 1-(3,3-dimethylaminopropyl)-3-ethylcarbodiimide, 1,3-dicyclohexylcarbodiimide, diphenylphosphoryl azide, diethyl cyanophosphate or carbonylimidazole. The inert solvent includes, for example, alcohols (e.g., methanol and ethanol), ethers (e.g., diethyl ether and tetrahydrofuran), hydrocarbons (e.g., toluene and benzene), halogenated carbonaceous solvents (e.g., chloroform and dichloromethane), dimethyl-formamide, acetonitrile, water and a mixed solvent thereof.

[0013]

[Step 2]

Compound (3) can be deprotected in the presence or absence of an acid in an inert solvent to give compound (4).

The deprotection of compound (3) can be carried out using the method described in Protective Groups in Organic Synthesis, by Theodora W. Greene and Peter G. M. Wuts.

[0014]

[Step 3]

Compound (4) can be coupled with compound (5) in the presence or absence of a base in an inert solvent to convert to compound (6). In case where Y^1 includes a protected amino group, acylation of the amino group can be carried out after deprotection in the presence or absence of a base in an inert solvent.

The base includes, for example, organic amines (e.g., triethylamine, diisopropylethylamine, pyridine and N-methylmorpholine) and inorganic bases (e.g., potassium carbonate and sodium bicarbonate). The coupling includes, for example, an amidation via an acid halide(e.g., an acid chloride and an acid bromide), an amidation via a mixed acid anhydride using ethyl chlorocarbonate, isobutyl chlorocarbonate, etc., and an amidation using a coupling agent such as 1-(3,3-dimethylaminopropyl)-3-ethylcarbodiimide, 1,3-dicyclohexylcarbodiimide, diphenylphosphoryl azide, diethyl cyanophosphate or carbonylimidazole. The inert solvent includes, for example, alcohols (e.g., methanol and ethanol), ethers (e.g., diethyl ether and tetrahydrofuran), hydrocarbons (e.g., toluene and benzene), halogenated carbonaceous solvents (e.g., chloroform and dichloromethane), dimethyl-formamide, acetonitrile, water and a mixed solvent thereof. The protected amino group is a protected amino group described in Protective Groups in Organic Synthesis, by Theodora W. Greene and Peter G. M. Wuts; and examples of which are a t-butoxycarbonylamino group

and a benzyloxycarbonylamino group. The deprotection is a deprotection of an amino group carried out according to the method described in Protective Groups in Organic Synthesis, by Theodora W. Greene and Peter G. M. Wuts. The acylation includes, for example, an acylation via an acid halide(e.g., an acid chloride and an acid bromide), an acylation using an acid anhydride (e.g., acetic anhydride), an acylation via a mixed acid anhydride using ethyl chlorocarbonate, isobutyl chlorocarbonate, etc., and an acylation using a coupling agent (e.g., 1-(3,3-dimethylaminopropyl)-3-ethylcarbodiimide, 1,3-dicyclohexylcarbodiimide, diphenylphosphoryl azide, diethyl cyanophosphate and carbonylimidazole).

[0015]

[Step 4]

Deprotection of a guanidino group can be carried out in the presence or absence of an acid in an inert solvent to give compound (6) of the present invention.

The deprotection of the guanidino group of the compound can be carried out using the method described in Protective Groups in Organic Synthesis, by Theodora W. Greene and Peter G. M. Wuts.

[0016]

[Embodiments]

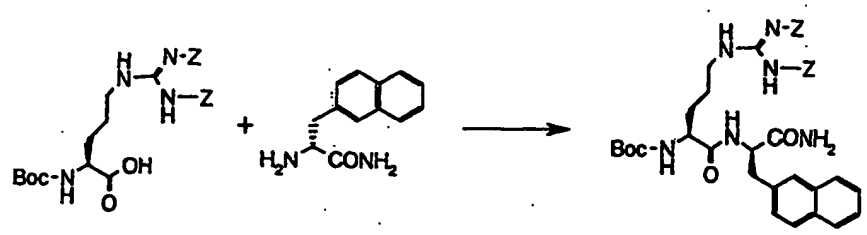
The present invention is illustrated in more detail with reference to the following examples; however, the present invention is in no way limited to

these examples (in the following formulae, Boc is a t-butylcarbonyl group, Z is a benzyloxycarbonyl group and Ac is an acetyl group).

Example 1 [Synthesis of compound 224 in Table 1]

[0017]

[Formula 4]



intermediate 1 intermediate 2 intermediate 3

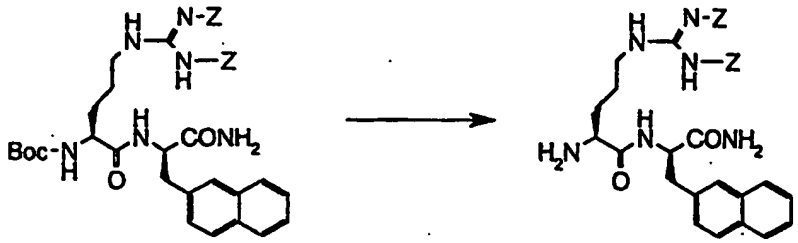
[0018]

(1) In 20 mL of dimethylformamide were dissolved 2.16 g of intermediate 1, 1.00 g of intermediate 2, 0.92 g of 1-hydroxybenzotriazole monohydrate and 0.42 g of N-methylmorpholine, and then 0.96 g of 1-(3,3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride was added with ice cooling. The temperature was slowly elevated to room temperature, followed by stirring for 3 days. The reaction solution was poured into a mixed solvent of ethyl acetate and water and, after separation of the solution, the organic layer was washed with 5 % aqueous potassium hydrogensulfate solution, a saturated aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution, successively. After

drying over anhydrous sodium sulfate, the drying agent was removed by filtration, followed by concentration under reduced pressure. The resulting crystals were recrystallized from ethyl acetate to give 2.27 g of intermediate 3.

[0019]

[Formula 5]



intermediate 3 intermediate 4

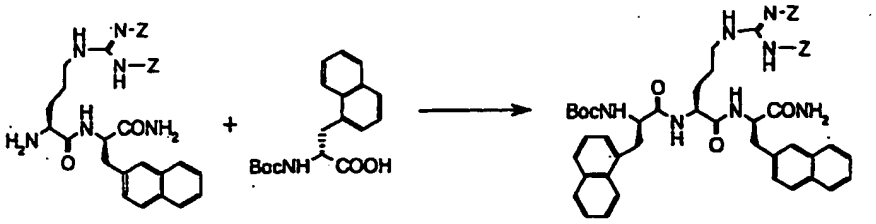
[0020]

(2) In 15 mL of methylene chloride was dissolved 1.50 g of intermediate 3 obtained in (1), and 15 mL of trifluoroacetic acid was added thereto, followed by stirring at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, and a saturated aqueous sodium bicarbonate solution was poured, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the drying agent was removed by filtration, followed by concentration under reduced pressure to give a crude intermediate 4, which was then used for the next

reaction without purification.

[0021]

[Formula 6]



intermediate 4 intermediate 5 intermediate 6

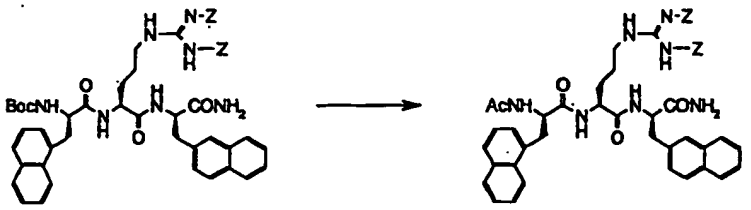
[0022]

(3) In 15 mL of dimethylformamide were dissolved 0.42 g of intermediate 4 obtained in (2), 0.24 g of intermediate 5 and 0.16 g of 1-hydroxybenzotriazole monohydrate, and then 0.16 g of 1-(3,3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride was added with ice cooling. The temperature was slowly elevated to room temperature, followed by stirring overnight. The reaction solution was poured into a mixed solvent of ethyl acetate and water and, after separation of the solution, the organic layer was washed with 5 % aqueous potassium hydrogensulfate solution, a saturated aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution, successively. After drying over anhydrous sodium sulfate, the drying agent was removed by filtration, followed by concentration under reduced pressure. The

residue was crystallized from ethyl acetate to give 0.43 g of intermediate 6.

[0023]

[Formula 7]



intermediate 6 intermediate 7

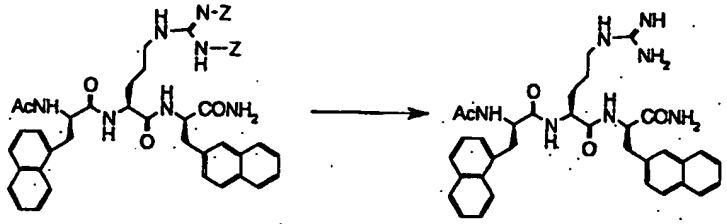
[0024]

(4) In 5 mL of methylene chloride was dissolved 0.40 g of intermediate 6 obtained in (3), and 5 mL of trifluoroacetic acid was added thereto, followed by stirring at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, and a saturated aqueous sodium bicarbonate solution was poured, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the drying agent was removed by filtration, followed by concentration under reduced pressure. The residue was dissolved in 3 mL of methylene chloride, and 1 mL of a methylene chloride solution of 48 mg of acetic anhydride and 37 mg of pyridine was added, followed by stirring at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure and, after pouring ethyl acetate, washed with water, 5 %

aqueous potassium hydrogensulfate solution, a saturated aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution, successively. After drying over anhydrous sodium sulfate, the drying agent was removed by filtration, followed by concentration under reduced pressure. The residue was crystallized from ethyl acetate to give 0.28 g of intermediate 7.

[0025]

[Formula 8]



intermediate 7 compound 224

[0026]

(5) In 10 mL of methanol was dissolved 0.28 g of intermediate 7 obtained in (4), and 100 mg of 20 % palladium hydroxide-activated carbon was added thereto, followed by stirring under a hydrogen atmosphere for 2 days. The reaction solution was filtered through Celite to remove the solid, and concentrated under reduced pressure. The residue was dissolved in 5 mL of methanol, 0.10 mL of 4M hydrogen chloride - ethyl acetate solution was added thereto and, after concentration under reduced pressure, solidification in

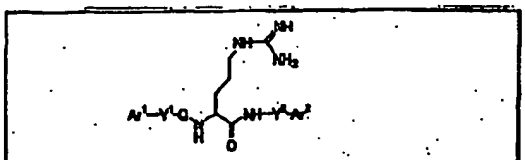
ethyl acetate gave 0.18 g of hydrochloride of compound 224.

The structures and physical property data of the present compound and the compounds prepared similarly are shown in Table 1.

[0027]

[Table 1]

Table 1



Comp.No	Ar^1-Y^1	Q	Y^2-Ar^2	$(M+1)^{+1}$
001	form(1)	CO	form(a)	501.3
002	form(1)	CO	form(b)	501.3
003	form(1)	CO	form(c)	515.3
004	form(1)	CO	form(d)	515.3
005	form(1)	CO	form(e)	551.3
006	form(1)	CO	form(f)	551.3
007	form(1)	CO	form(g)	551.3
008	form(1)	CO	form(h)	551.3
009	form(1)	CO	form(i)	502.3
010	form(1)	CO	form(j)	502.3
011	form(1)	CO	form(k)	491.3
012	form(1)	CO	form(l)	491.3
013	form(2)	CO	form(a)	501.3
014	form(2)	CO	form(b)	501.3
015	form(2)	CO	form(c)	515.3
016	form(2)	CO	form(d)	515.3
017	form(2)	CO	form(e)	551.3
018	form(2)	CO	form(f)	551.3
019	form(2)	CO	form(g)	551.3
020	form(2)	CO	form(h)	551.3
021	form(2)	CO	form(i)	502.3
022	form(2)	CO	form(j)	502.3
023	form(2)	CO	form(k)	491.3
024	form(2)	CO	form(l)	491.3
025	form(3)	CO	form(a)	503.3
026	form(3)	CO	form(b)	503.3
027	form(3)	CO	form(c)	517.3
028	form(3)	CO	form(d)	517.3
029	form(3)	CO	form(e)	553.3
030	form(3)	CO	form(f)	553.3
031	form(3)	CO	form(g)	553.3
032	form(3)	CO	form(h)	553.3
033	form(3)	CO	form(i)	504.3
034	form(3)	CO	form(j)	504.3
035	form(3)	CO	form(k)	493.3
036	form(3)	CO	form(l)	493.3
037	form(4)	CO	form(a)	629.4
038	form(4)	CO	form(b)	629.4
039	form(4)	CO	form(c)	643.4
040	form(4)	CO	form(d)	643.4

[0028]

[Table 2]

Table 1

041	form(4)	CO	form(e)	679.3
042	form(4)	CO	form(f)	679.3
043	form(4)	CO	form(g)	679.3
044	form(4)	CO	form(h)	679.3
045	form(4)	CO	form(i)	630.4
046	form(4)	CO	form(j)	630.4
047	form(4)	CO	form(k)	619.4
048	form(4)	CO	form(l)	619.4
049	form(5)	CO	form(a)	629.4
050	form(5)	CO	form(b)	629.4
051	form(5)	CO	form(c)	643.4
052	form(5)	CO	form(d)	643.4
053	form(5)	CO	form(e)	679.3
054	form(5)	CO	form(f)	679.3
055	form(5)	CO	form(g)	679.3
056	form(5)	CO	form(h)	679.3
057	form(5)	CO	form(i)	630.4
058	form(5)	CO	form(j)	630.4
059	form(5)	CO	form(k)	619.4
060	form(5)	CO	form(l)	619.4
061	form(6)	CO	form(a)	629.4
062	form(6)	CO	form(b)	629.4
063	form(6)	CO	form(c)	643.4
064	form(6)	CO	form(d)	643.4
065	form(6)	CO	form(e)	679.3
066	form(6)	CO	form(f)	679.3
067	form(6)	CO	form(g)	679.3
068	form(6)	CO	form(h)	679.3
069	form(6)	CO	form(i)	630.4
070	form(6)	CO	form(j)	630.4
071	form(6)	CO	form(k)	619.4
072	form(6)	CO	form(l)	619.4
073	form(7)	SO_2	form(a)	511.2
074	form(7)	SO_2	form(b)	511.2
075	form(7)	SO_2	form(c)	525.3
076	form(7)	SO_2	form(d)	525.3
077	form(7)	SO_2	form(e)	561.3
078	form(7)	SO_2	form(f)	561.3
079	form(7)	SO_2	form(g)	561.3
080	form(7)	SO_2	form(h)	561.3
081	form(7)	SO_2	form(i)	512.2
082	form(7)	SO_2	form(j)	512.3
083	form(7)	SO_2	form(k)	501.2
084	form(7)	SO_2	form(l)	501.2

[0029]

[Table 3]

Table 1

085	form(8)	SO_2	form(a)	554.3
086	form(8)	SO_2	form(b)	554.3
087	form(8)	SO_2	form(c)	568.3
088	form(8)	SO_2	form(d)	568.3
089	form(8)	SO_2	form(e)	604.3
090	form(8)	SO_2	form(f)	604.3
091	form(8)	SO_2	form(g)	604.3
092	form(8)	SO_2	form(h)	604.3
093	form(8)	SO_2	form(i)	555.3
094	form(8)	SO_2	form(j)	555.3
095	form(8)	SO_2	form(k)	544.3
096	form(8)	SO_2	form(l)	544.3
097	form(1)	CO	form(m)	487.2
098	form(1)	CO	form(n)	487.2
099	form(1)	CO	form(o)	502.3
100	form(1)	CO	form(p)	502.3
101	form(1)	CO	form(q)	502.3
102	form(1)	CO	form(r)	557.2
103	form(1)	CO	form(s)	577.2
104	form(1)	CO	form(t)	577.2
105	form(2)	CO	form(m)	487.2
106	form(2)	CO	form(n)	487.3
107	form(2)	CO	form(o)	502.3
108	form(2)	CO	form(p)	502.3
109	form(2)	CO	form(q)	502.3
110	form(2)	CO	form(r)	557.2
111	form(2)	CO	form(s)	577.2
112	form(2)	CO	form(t)	577.2
113	form(3)	CO	form(m)	489.3
114	form(3)	CO	form(n)	489.3
115	form(3)	CO	form(o)	504.3
116	form(3)	CO	form(p)	504.3
117	form(3)	CO	form(q)	504.3
118	form(3)	CO	form(r)	559.2
119	form(3)	CO	form(s)	579.3
120	form(3)	CO	form(t)	579.3
121	form(4)	CO	form(m)	615.3
122	form(4)	CO	form(n)	615.3
123	form(4)	CO	form(o)	630.4
124	form(4)	CO	form(p)	630.3
125	form(4)	CO	form(q)	630.3
126	form(4)	CO	form(r)	685.3
127	form(4)	CO	form(s)	705.3
128	form(4)	CO	form(t)	705.3

[0030]

[Table 4]

Table 1

129	form(5)	CO	form(m)	615.3
130	form(5)	CO	form(n)	615.3
131	form(5)	CO	form(o)	630.3
132	form(5)	CO	form(p)	630.3
133	form(5)	CO	form(q)	630.4
134	form(5)	CO	form(r)	685.2
135	form(5)	CO	form(s)	705.3
136	form(5)	CO	form(t)	705.3
137	form(6)	CO	form(m)	615.3
138	form(6)	CO	form(n)	615.3
139	form(6)	CO	form(o)	630.3
140	form(6)	CO	form(p)	630.3
141	form(6)	CO	form(q)	630.3
142	form(6)	CO	form(r)	685.2
143	form(6)	CO	form(s)	705.3
144	form(6)	CO	form(t)	705.3
145	form(7)	SO_2	form(m)	497.8
146	form(7)	SO_2	form(n)	497.2
147	form(7)	SO_2	form(p)	512.2
148	form(7)	SO_2	form(r)	567.1
149	form(7)	SO_2	form(s)	587.2
150	form(7)	SO_2	form(t)	587.2
151	form(8)	SO_2	form(m)	540.3
152	form(8)	SO_2	form(n)	540.3
153	form(8)	SO_2	form(p)	555.2
154	form(8)	SO_2	form(r)	610.2
155	form(8)	SO_2	form(s)	630.3
156	form(8)	SO_2	form(t)	630.3
157	form(9)	CO	form(a)	510.3
158	form(9)	CO	form(b)	510.3
159	form(9)	CO	form(c)	524.3
160	form(9)	CO	form(d)	524.3
161	form(9)	CO	form(e)	560.3
162	form(9)	CO	form(f)	560.3
163	form(9)	CO	form(g)	560.3
164	form(9)	CO	form(h)	560.3
165	form(9)	CO	form(i)	511.3
166	form(9)	CO	form(j)	511.3
167	form(9)	CO	form(k)	500.3
168	form(9)	CO	form(l)	500.3
169	form(10)	CO	form(a)	510.3
170	form(10)	CO	form(b)	510.3
171	form(10)	CO	form(c)	524.3
172	form(10)	CO	form(d)	524.3

[0031]

[Table 5]

Table 1

173	form(10)	CO	form(e)	560.3
174	form(10)	CO	form(f)	560.3
175	form(10)	CO	form(g)	560.3
176	form(10)	CO	form(h)	560.3
177	form(10)	CO	form(i)	511.3
178	form(10)	CO	form(j)	511.3
179	form(10)	CO	form(k)	500.3
180	form(10)	CO	form(l)	500.3
181	form(11)	CO	form(a)	524.3
182	form(11)	CO	form(b)	524.3
183	form(11)	CO	form(c)	538.3
184	form(11)	CO	form(d)	538.3
185	form(11)	CO	form(e)	574.3
186	form(11)	CO	form(f)	574.3
187	form(11)	CO	form(g)	574.3
188	form(11)	CO	form(h)	574.3
189	form(11)	CO	form(i)	525.3
190	form(11)	CO	form(j)	525.3
191	form(11)	CO	form(k)	514.3
192	form(11)	CO	form(l)	514.3
193	form(12)	CO	form(a)	524.3
194	form(12)	CO	form(b)	524.3
195	form(12)	CO	form(c)	538.3
196	form(12)	CO	form(d)	538.3
197	form(12)	CO	form(e)	574.3
198	form(12)	CO	form(f)	574.3
199	form(12)	CO	form(g)	574.3
200	form(12)	CO	form(h)	574.3
201	form(12)	CO	form(i)	525.3
202	form(12)	CO	form(j)	525.3
203	form(12)	CO	form(k)	514.3
204	form(12)	CO	form(l)	514.3
205	form(13)	CO	form(a)	560.3
206	form(13)	CO	form(b)	560.3
207	form(13)	CO	form(c)	574.3
208	form(13)	CO	form(d)	574.3
209	form(13)	CO	form(e)	610.3
210	form(13)	CO	form(f)	610.3
211	form(13)	CO	form(g)	610.3
212	form(13)	CO	form(h)	610.3
213	form(13)	CO	form(i)	561.3
214	form(13)	CO	form(j)	561.3
215	form(13)	CO	form(k)	550.3
216	form(13)	CO	form(l)	550.3
217	form(14)	CO	form(a)	560.3
218	form(14)	CO	form(b)	560.3

[0032]

[Table 6]

Table 1

219	form(14)	CO	form(c)	574.3
220	form(14)	CO	form(d)	574.3
221	form(14)	CO	form(e)	610.3
222	form(14)	CO	form(f)	610.3
223	form(14)	CO	form(g)	610.3
224	form(14)	CO	form(h)	610.3
225	form(14)	CO	form(i)	561.3
226	form(14)	CO	form(j)	561.3
227	form(14)	CO	form(k)	550.3
228	form(14)	CO	form(l)	550.3
229	form(15)	CO	form(a)	560.3
230	form(15)	CO	form(b)	560.3
231	form(15)	CO	form(c)	574.3
232	form(15)	CO	form(d)	574.3
233	form(15)	CO	form(e)	610.3
234	form(15)	CO	form(f)	610.3
235	form(15)	CO	form(g)	610.3
236	form(15)	CO	form(h)	610.3
237	form(15)	CO	form(i)	561.3
238	form(15)	CO	form(j)	561.3
239	form(15)	CO	form(k)	550.3
240	form(15)	CO	form(l)	550.3
241	form(16)	CO	form(a)	560.3
242	form(16)	CO	form(b)	560.3
243	form(16)	CO	form(c)	574.3
244	form(16)	CO	form(d)	574.3
245	form(16)	CO	form(e)	610.3
246	form(16)	CO	form(f)	610.3
247	form(16)	CO	form(g)	610.3
248	form(16)	CO	form(h)	610.3
249	form(16)	CO	form(i)	561.3
250	form(16)	CO	form(j)	561.3
251	form(16)	CO	form(k)	550.3
252	form(16)	CO	form(l)	550.3
253	form(9)	CO	form(m)	496.3
254	form(9)	CO	form(n)	496.3
255	form(9)	CO	form(o)	511.3
256	form(9)	CO	form(p)	511.3
257	form(9)	CO	form(q)	511.3
258	form(9)	CO	form(r)	586.2
259	form(9)	CO	form(s)	586.3
260	form(9)	CO	form(t)	586.3
261	form(10)	CO	form(m)	496.3
262	form(10)	CO	form(n)	496.3
263	form(10)	CO	form(o)	511.3
264	form(10)	CO	form(p)	511.3

[0033]

[Table 7]

Table 1

265	form(10)	CO	form(q)	511.3
266	form(10)	CO	form(r)	566.2
267	form(10)	CO	form(s)	586.3
268	form(10)	CO	form(t)	586.3
269	form(11)	CO	form(m)	510.3
270	form(11)	CO	form(n)	510.3
271	form(11)	CO	form(o)	525.3
272	form(11)	CO	form(p)	525.3
273	form(11)	CO	form(q)	525.3
274	form(11)	CO	form(r)	580.2
275	form(11)	CO	form(s)	600.3
276	form(11)	CO	form(t)	600.3
277	form(12)	CO	form(m)	510.3
278	form(12)	CO	form(n)	510.3
279	form(12)	CO	form(o)	525.3
280	form(12)	CO	form(p)	525.3
281	form(12)	CO	form(q)	525.3
282	form(12)	CO	form(r)	580.2
283	form(12)	CO	form(s)	600.3
284	form(12)	CO	form(t)	600.3
285	form(13)	CO	form(m)	546.3
286	form(13)	CO	form(n)	546.3
287	form(13)	CO	form(o)	561.3
288	form(13)	CO	form(p)	561.3
289	form(13)	CO	form(q)	561.3
290	form(13)	CO	form(r)	616.3
291	form(13)	CO	form(s)	636.4
292	form(13)	CO	form(t)	636.4
293	form(14)	CO	form(m)	546.3
294	form(14)	CO	form(n)	546.3
295	form(14)	CO	form(o)	561.3
296	form(14)	CO	form(p)	561.3
297	form(14)	CO	form(q)	561.3
298	form(14)	CO	form(r)	616.3
299	form(14)	CO	form(s)	616.4
300	form(14)	CO	form(t)	636.4
301	form(15)	CO	form(m)	546.3
302	form(15)	CO	form(n)	546.3
303	form(15)	CO	form(o)	561.2
304	form(15)	CO	form(p)	561.3
305	form(15)	CO	form(q)	561.3
306	form(15)	CO	form(r)	616.3
307	form(15)	CO	form(s)	636.4
308	form(15)	CO	form(t)	636.4
309	form(16)	CO	form(m)	546.3
310	form(16)	CO	form(n)	546.3

[0034]

[Table 8]

Table 1

311	form(16)	CO	form(o)	561.3
312	form(16)	CO	form(p)	561.3
313	form(16)	CO	form(q)	561.3
314	form(16)	CO	form(r)	616.3
315	form(16)	CO	form(s)	636.4
316	form(16)	CO	form(t)	636.4
317	form(17)	CO	form(a)	511.3
318	form(17)	CO	form(b)	511.3
319	form(17)	CO	form(c)	525.3
320	form(17)	CO	form(d)	525.3
321	form(17)	CO	form(e)	561.3
322	form(17)	CO	form(f)	561.3
323	form(17)	CO	form(g)	561.3
324	form(17)	CO	form(h)	561.3
325	form(17)	CO	form(i)	512.3
326	form(17)	CO	form(j)	512.3
327	form(17)	CO	form(k)	501.3
328	form(17)	CO	form(l)	501.3
329	form(18)	CO	form(a)	511.3
330	form(18)	CO	form(b)	511.3
331	form(18)	CO	form(c)	525.3
332	form(18)	CO	form(d)	525.3
333	form(18)	CO	form(e)	561.3
334	form(18)	CO	form(f)	561.3
335	form(18)	CO	form(g)	561.3
336	form(18)	CO	form(h)	561.3
337	form(18)	CO	form(i)	512.3
338	form(18)	CO	form(j)	512.3
339	form(18)	CO	form(k)	501.3
340	form(18)	CO	form(l)	501.3
341	form(19)	CO	form(a)	500.3
342	form(19)	CO	form(b)	500.3
343	form(19)	CO	form(c)	514.3
344	form(19)	CO	form(d)	514.3
345	form(19)	CO	form(e)	550.3
346	form(19)	CO	form(f)	550.3
347	form(19)	CO	form(g)	550.3
348	form(19)	CO	form(h)	550.3
349	form(19)	CO	form(i)	501.3
350	form(19)	CO	form(j)	501.3
351	form(19)	CO	form(k)	490.3
352	form(19)	CO	form(l)	490.3
353	form(20)	CO	form(a)	500.3
354	form(20)	CO	form(b)	500.3
355	form(20)	CO	form(c)	514.3
356	form(20)	CO	form(d)	514.3

[0035]

[Table 9]

Table 1

357	form(20)	CO	form(e)	550.3
358	form(20)	CO	form(f)	550.3
359	form(20)	CO	form(g)	550.3
360	form(20)	CO	form(h)	550.3
361	form(20)	CO	form(i)	501.3
362	form(20)	CO	form(j)	501.3
363	form(20)	CO	form(k)	490.3
364	form(20)	CO	form(l)	490.3
365	form(21)	CO	form(a)	496.3
366	form(21)	CO	form(b)	496.3
367	form(21)	CO	form(c)	510.3
368	form(21)	CO	form(d)	510.3
369	form(21)	CO	form(e)	546.3
370	form(21)	CO	form(f)	546.3
371	form(21)	CO	form(g)	546.3
372	form(21)	CO	form(h)	546.3
373	form(21)	CO	form(i)	497.3
374	form(21)	CO	form(j)	497.3
375	form(21)	CO	form(k)	486.3
376	form(21)	CO	form(l)	486.3
377	form(22)	CO	form(a)	496.3
378	form(22)	CO	form(b)	496.3
379	form(22)	CO	form(c)	510.3
380	form(22)	CO	form(d)	510.3
381	form(22)	CO	form(e)	546.3
382	form(22)	CO	form(f)	546.3
383	form(22)	CO	form(g)	546.3
384	form(22)	CO	form(h)	546.3
385	form(22)	CO	form(i)	497.3
386	form(22)	CO	form(j)	497.3
387	form(22)	CO	form(k)	486.3
388	form(22)	CO	form(l)	486.3
389	form(23)	CO	form(a)	511.3
390	form(23)	CO	form(b)	511.3
391	form(23)	CO	form(c)	525.3
392	form(23)	CO	form(d)	525.3
393	form(23)	CO	form(e)	561.3
394	form(23)	CO	form(f)	561.3
395	form(23)	CO	form(g)	561.3
396	form(23)	CO	form(h)	561.3
397	form(23)	CO	form(i)	512.3
398	form(23)	CO	form(j)	512.3
399	form(23)	CO	form(k)	501.3
400	form(23)	CO	form(l)	501.3
401	form(24)	CO	form(a)	511.3
402	form(24)	CO	form(b)	511.3

[0036]

[Table 10]

Table 1

403	form(24)	CO	form(c)	525.3
404	form(24)	CO	form(d)	525.3
405	form(24)	CO	form(e)	561.3
406	form(24)	CO	form(f)	561.3
407	form(24)	CO	form(g)	561.3
408	form(24)	CO	form(h)	561.3
409	form(24)	CO	form(i)	512.3
410	form(24)	CO	form(j)	512.3
411	form(24)	CO	form(k)	501.3
412	form(24)	CO	form(l)	501.3
413	form(17)	CO	form(m)	497.3
414	form(17)	CO	form(n)	497.3
415	form(17)	CO	form(o)	512.3
416	form(17)	CO	form(p)	512.3
417	form(17)	CO	form(q)	512.3
418	form(17)	CO	form(r)	567.2
419	form(17)	CO	form(s)	587.3
420	form(17)	CO	form(t)	587.3
421	form(18)	CO	form(m)	497.3
422	form(18)	CO	form(n)	497.3
423	form(18)	CO	form(o)	512.3
424	form(18)	CO	form(p)	512.3
425	form(18)	CO	form(q)	512.3
426	form(18)	CO	form(r)	567.2
427	form(18)	CO	form(s)	587.3
428	form(18)	CO	form(t)	587.3
429	form(19)	CO	form(m)	486.3
430	form(19)	CO	form(n)	486.3
431	form(19)	CO	form(o)	501.3
432	form(19)	CO	form(p)	501.3
433	form(19)	CO	form(q)	501.3
434	form(19)	CO	form(r)	556.2
435	form(19)	CO	form(s)	576.3
436	form(19)	CO	form(t)	576.3
437	form(20)	CO	form(m)	486.3
438	form(20)	CO	form(n)	486.3
439	form(20)	CO	form(o)	501.3
440	form(20)	CO	form(p)	501.3
441	form(20)	CO	form(q)	501.3
442	form(20)	CO	form(r)	556.2
443	form(20)	CO	form(s)	576.3
444	form(20)	CO	form(t)	576.3
445	form(21)	CO	form(m)	482.2
446	form(21)	CO	form(n)	482.2
447	form(21)	CO	form(o)	497.3
448	form(21)	CO	form(p)	497.3

[0037]

[Table 11]

Table 1

449	form(21)	CO	form(q)	497.3
450	form(21)	CO	form(r)	552.2
451	form(21)	CO	form(s)	572.3
452	form(21)	CO	form(t)	572.3
453	form(22)	CO	form(m)	482.3
454	form(22)	CO	form(n)	482.3
455	form(22)	CO	form(o)	497.3
456	form(22)	CO	form(p)	497.3
457	form(22)	CO	form(q)	497.3
458	form(22)	CO	form(r)	552.2
459	form(22)	CO	form(s)	572.3
460	form(22)	CO	form(t)	572.3
461	form(23)	CO	form(m)	497.3
462	form(23)	CO	form(n)	497.3
463	form(23)	CO	form(o)	512.3
464	form(23)	CO	form(p)	512.3
465	form(23)	CO	form(q)	512.3
466	form(23)	CO	form(r)	567.2
467	form(23)	CO	form(s)	587.3
468	form(23)	CO	form(t)	587.3
469	form(24)	CO	form(m)	497.3
470	form(24)	CO	form(n)	497.3
471	form(24)	CO	form(o)	512.3
472	form(24)	CO	form(p)	512.3
473	form(24)	CO	form(q)	512.4
474	form(24)	CO	form(r)	567.2
475	form(24)	CO	form(s)	587.3
476	form(24)	CO	form(t)	587.3
477	form(25)	CO	form(a)	511.3
478	form(25)	CO	form(b)	511.3
479	form(25)	CO	form(c)	525.3
480	form(25)	CO	form(d)	525.3
481	form(25)	CO	form(e)	581.3
482	form(25)	CO	form(f)	581.3
483	form(25)	CO	form(g)	581.3
484	form(25)	CO	form(h)	581.3
485	form(25)	CO	form(i)	512.3
486	form(25)	CO	form(j)	512.3
487	form(25)	CO	form(k)	501.3
488	form(25)	CO	form(l)	501.3
489	form(26)	CO	form(a)	566.2
490	form(26)	CO	form(b)	566.2
491	form(26)	CO	form(c)	580.2
492	form(26)	CO	form(d)	580.2
493	form(26)	CO	form(e)	616.3
494	form(26)	CO	form(f)	616.3

[0038]

[Table 12]

Table 1

495	form(26)	CO	form(g)	616.3
496	form(26)	CO	form(h)	616.3
497	form(26)	CO	form(i)	587.2
498	form(26)	CO	form(j)	587.2
499	form(26)	CO	form(k)	556.2
500	form(26)	CO	form(l)	556.2
501	form(27)	CO	form(a)	586.3
502	form(27)	CO	form(b)	586.3
503	form(27)	CO	form(c)	600.3
504	form(27)	CO	form(d)	600.3
505	form(27)	CO	form(e)	636.4
506	form(27)	CO	form(f)	636.4
507	form(27)	CO	form(g)	636.4
508	form(27)	CO	form(h)	636.4
509	form(27)	CO	form(i)	587.3
510	form(27)	CO	form(j)	587.3
511	form(27)	CO	form(k)	576.3
512	form(27)	CO	form(l)	576.3
513	form(28)	CO	form(a)	586.3
514	form(28)	CO	form(b)	586.3
515	form(28)	CO	form(c)	600.3
516	form(28)	CO	form(d)	600.3
517	form(28)	CO	form(e)	636.4
518	form(28)	CO	form(f)	636.4
519	form(28)	CO	form(g)	636.3
520	form(28)	CO	form(h)	636.4
521	form(28)	CO	form(i)	587.3
522	form(28)	CO	form(j)	587.3
523	form(28)	CO	form(k)	576.2
524	form(28)	CO	form(l)	576.3
525	form(25)	CO	form(m)	497.3
526	form(25)	CO	form(n)	497.3
527	form(25)	CO	form(o)	512.3
528	form(25)	CO	form(p)	512.3
529	form(25)	CO	form(q)	512.3
530	form(25)	CO	form(r)	567.2
531	form(25)	CO	form(s)	587.3
532	form(25)	CO	form(t)	587.3
533	form(26)	CO	form(m)	552.2
534	form(26)	CO	form(n)	552.2
535	form(26)	CO	form(o)	567.2
536	form(26)	CO	form(q)	587.2
537	form(26)	CO	form(r)	622.2
538	form(26)	CO	form(s)	642.3
539	form(26)	CO	form(t)	642.3
540	form(27)	CO	form(m)	572.3

[0039]

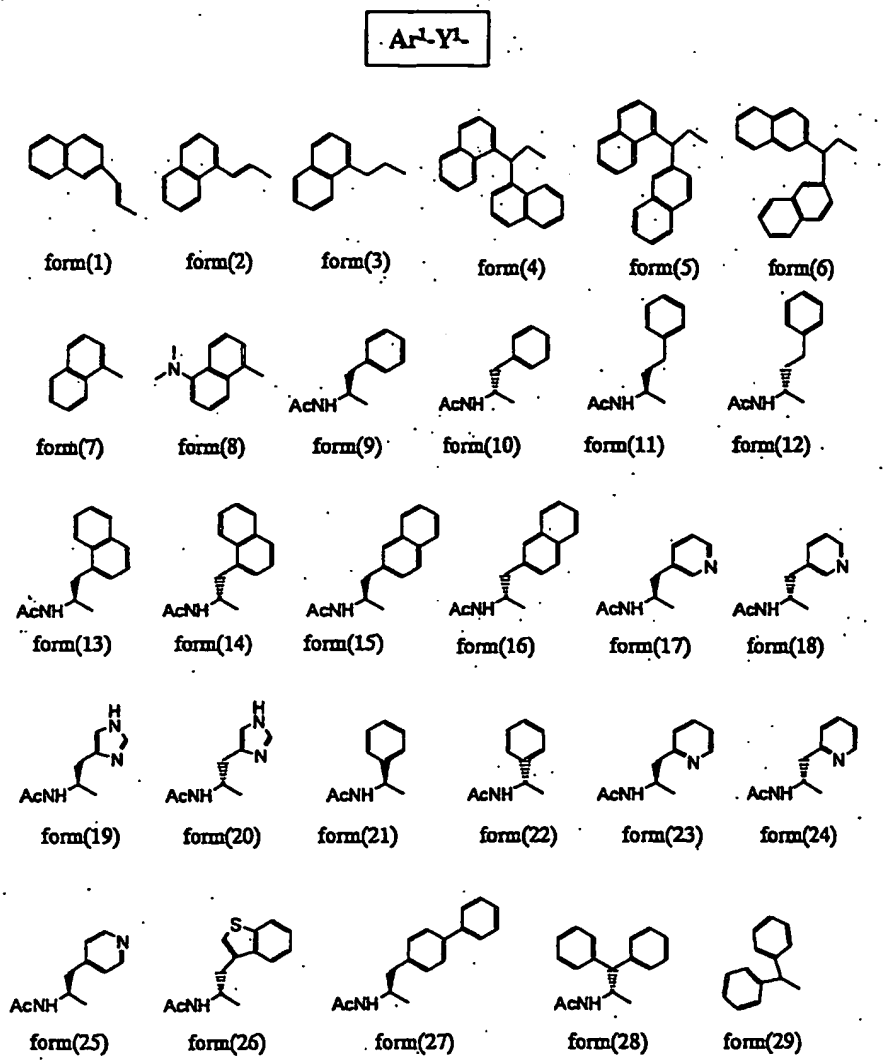
[Table 13]

Table 1

541	form(27)	CO	form(n)	572.3
542	form(27)	CO	form(o)	587.2
543	form(27)	CO	form(p)	587.3
544	form(27)	CO	form(q)	587.3
545	form(27)	CO	form(r)	642.3
546	form(27)	CO	form(s)	662.3
547	form(27)	CO	form(t)	662.3
548	form(28)	CO	form(m)	572.2
549	form(28)	CO	form(n)	572.2
550	form(28)	CO	form(o)	587.3
551	form(28)	CO	form(p)	587.3
552	form(28)	CO	form(q)	587.3
553	form(28)	CO	form(r)	642.3
554	form(28)	CO	form(s)	662.3
555	form(28)	CO	form(t)	662.3
556	form(29)	CO	form(u)	*2
557	form(29)	CO	form(w)	*3
558	form(29)	CO	form(x)	*4
559	form(4)	CO	form(u)	*5
*1:ESIMS(Pos)				
*2:HRMS(FAB) calcd for $C_{31}H_{35}N_7O_3$ 554.2880, fo				
*3:HRMS(FAB) calcd for $C_{33}H_{39}N_7O_3$ 582.3193, fo				
*4:HRMS(FAB) calcd for $C_{31}H_{36}N_6O_3$ 541.2927, fo				
*5:HRMS(FAB) calcd for $C_{40}H_{41}N_7O_3$ 668.3350, fo				

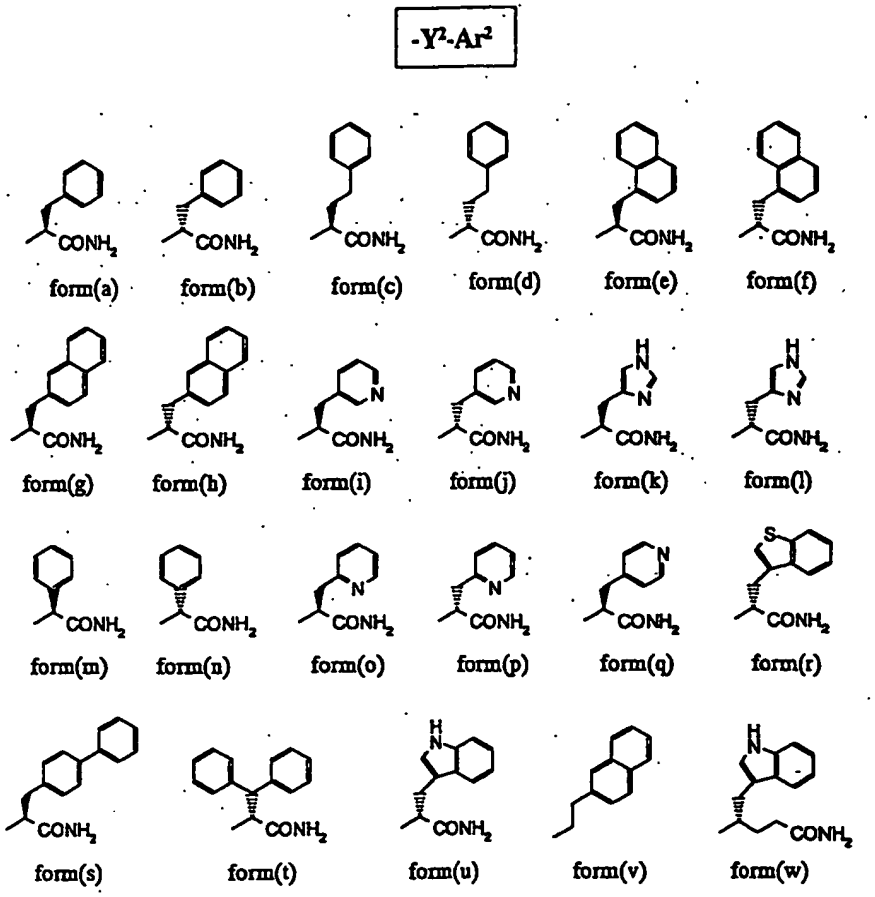
[0040]

[Formula 9]



[0041]

[Formula 10]



[0042]

Experiment [MC_4 receptor Binding Assay]

MC_4 receptor binding assay was carried out according to the method described in Pharmacology & Toxicology, 79, 161-165, 1996. HEK-293 cell membranes expressing the human MC_4 receptor were purchased from Biolinks Co. The cell membranes were homogenized in a 50 mM Tris hydrochloric acid buffer solution (pH 7.4)

containing 2 mM ethylenediamine tetraacetic acid, 10 mM calcium chloride and 100 μM phenylmethanesulfonyl-fluoride. The homogenate was centrifuged at 48,000 x g for 20 minutes at 4°C. The precipitate obtained by centrifugation was again homogenized in the same buffer solution, and the homogenate was centrifuged at 48,000 x g for 20 minutes at 4°C. This procedure was repeated twice. The precipitate was suspended in 50 mM Tris hydrochloric acid buffer solution (pH 7.4) containing 2 mM ethylenediamine tetraacetic acid, 10 mM calcium chloride, 100 μM phenylmethanesulfonylfluoride and 0.1 % bovine serum albumin to adjust to a protein concentration of 100 μg/ml to give a crude membrane preparation which was used for the binding assay. The crude membrane preparation (0.25 ml, 25 μg protein) was reacted with [^{125}I]Nle^{4}-D-Phe^{7}-α-MSH (final concentration; 0.2 nM) at 25°C for 120 minutes. After the completion of the reaction, the reaction solution was filtered under suction on GF/C glass filter presoaked for 2 hours in 50 mM Tris hydrochloric acid buffer solution (pH 7.4) containing 0.5 % bovine serum with the use of a cell harvester for receptor binding assay. The radioactivity on the filter paper was measured in a gamma-counter. The binding in the presence of 1 μM Nle^{4}-D-Phe^{7}-α-MSH was defined as non-specific binding. Specific binding was obtained by subtracting the non-specific binding from the total binding, which was the binding in the absence of 1 μM

Nle^4-D-Phe^7-α-MSH. Test compound was dissolved in 100 % DMSO, and added simultaneously with [^{125}I]Nle^4-D-Phe^7-α-MSH to the membrane preparation. The IC_{50} value was calculated from the inhibition curve in the concentration of 10^{-9} - 10^{-5}.

As a result, for example, the IC_{50} value of compound 224 was 690 nM.

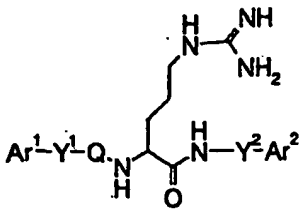
[Title of Document] Abstract

[Abstract]

[Problem] There are provided peptidergic ligands which have the affinity and specificity to MC_4 receptor.

[Solving Means] An arginine derivative represented by the formula:

[Formula 11]



[wherein Ar^1 and Ar^2 may be the same or different, and are each a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, or a heteroaromatic ring containing one or more of nitrogen, oxygen and sulfur atoms; Y^1 is a C_{1-5} alkylene group which optionally contains a carbon atom substituted with a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, or a C_{1-10} acylamino group, and optionally contains a double bond in the main chain, or a single bond; Q is a carbonyl group or a sulfonyl group; Y^2 is a C_{1-5} alkylene group which optionally contains a carbon atom substituted with a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, a hydroxyl

group, a carbamoyl group, or an amide group having one or two of C_{1-5} alkyl groups on the nitrogen atom], or a pharmaceutically acceptable salt thereof.

[Selective Drawing] None